EFFECT OF MATERNAL VOICE ON PHYSIOLOGICAL AND BEHAVIORAL MEASURES IN PREMATURE INFANTS: A RANDOMIZED CONTROLLED TRIAL

BY

DR NURUL AMANI BINTI ABD GHANI

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Bismillah Al Rahman Al Rahim.

All praises to Allah whom with His willing and planning allows me to complete this dissertation.

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ABBREVIATIONS

CGA	Corrected gestational age
NICU	Neonatal intensive care unit
SPO2	Oxygen saturation

ABSTRAK

Pengenalan

Bayi pramatang kehilangan hubungan yang signifikan dengan ibu mereka semasa perkembangan postnatal dan dijaga dalam persekitaran hospital yang mendedahkan mereka kepada rangsangan berlebihan dari persekitaran NICU. Mereka bukan sahaja terhindar dari perlindungan dari dalam rahim, mereka juga kekal dalam inkubator tertutup di mana rangsangan sentuhan dan deria adalah terhad dan juga kehilangan aspek kritikal untuk perkembangan normal iaitu suara ibu

Objektif

Tujuan kajian ini adalah untuk menentukan kesan suara ibu atau bunyi persekitaran NICU terhadap parameter fisiologi dan tingkah laku di kalangan bayi pra-matang.

Kaedah

Ini adalah kajian terkawal rawak selari yang dijalankan di NICU Hospital Sultanah Bahiyah, Alor Setar dari bulan Jun 2015 hingga November 2015. Kajian ini melibatkan semua bayi pra-matang dengan usia kandungan 27-35 minggu yang sudah menyusu susu sepenuhnya dan dijaga di dalam inkubator. Semua bayi ini dibahagikan secara rawak kepada dua kumpulan iaitu Intervensi dan Kawalan. Ibu mereka akan diminta untuk menyanyikan lullabies sesuai yang akan direkodkan untuk tempoh 10 minit. Bayi dalam kumpulan kawalan menerima penjagaan rutin NICU manakala bayi dalam kumpulan intervensi menerima penjagan rutin NICU berserta 10 minit pendedahan kepada rakaman suara ibu mereka setiap hari selama 14 hari. Semua bayi dalam kedua-dua kumpulan

telah dinilai dan diperhatikan untuk 30 minit setiap hari selama 14 hari. Kadar jantung, kadar pernafasan dan tahap ketepuan oksigen seperti yang dipaparkan pada monitor direkodkan setiap minit selama 30 minit. Skor tingkahlaku mereka (BIIP) telah diukur pada setiap 10 minit. Penambahan berat badan diukur selang sehari oleh penimbang digital yang seragam. Bayi telah dinilai selama 3 fasa: garis dasar 10 minit, intervensi 10 minit dan 10 minit selepas intervensi.

Keputusan

Seramai 138 pesakit selesai menjalani kajian. Terdapat pengurangan ketara kadar jantun dari masa ke masa [F = 5,071, p <0.05] dan kadar pernafasan median dari masa ke masa (Z = -7,27, p <0.01). Terdapat perbezaan yang signifikan dalam kadar pernafasan median dalam kumpulan intervensi (Z = -4,39, -4,23, -4,15, p <0.01) berbanding untuk kumpulan kawalan. Terdapat juga peningkatan yang ketara ketepuan oksigen dalam kumpulan intervensi (Z = -2,14, -2,39, -2,56 p <0.05). Tidak ada perbezaan yang signifikan dalam min berat badan kumpulan intervensi dan kumpulan kawalan [MD 0.30 (-1.9, 2.5), P> 0.05]. Tiada perubahan yang ketara skor tingkahlaku (BIIP) dengan mengambil kira masa [Z = -0.31, -0.36, -0.65 P >0.05].

Kesimpulan

Kajian ini menunjukkan bahawa pendedahan kepada suara ibu mempunyai kesan positif pada kadar degupan jantung, kadar pernafasan dan oksigen tepu bayi pramatang manakala tiada tindak balas yang buruk diperhatikan semasa campur tangan.

ABSTRACT

Introduction

Preterm infants lose significant contact with their mothers during prenatal development and nursed in hospital environment that exposed them to elevated stimulus from NICU environment. They are not only deprived from the protective properties of womb, they also remain in an enclosed incubator where touching and sensory stimulation are restricted which possibly a critical aspect for normal development, that is the mother's voice

Objective

The aim of this study is to determine the effect of maternal voice vs NICU environmental sounds on physiological and behavioral measures in premature infants.

Method

This is a parallel randomized control trial conducted in NICU Hospital Sultanah Bahiyah, Alor Setar from June 2015 to Nov 2015. This study involved all premature infants with corrected gestational age 27-35 weeks who is already on full feeding and nursed in incubator. All subjects were randomized into two groups that are Intervention and Control. Their mother will be asked to sing appropriate lullabies that will be recorded for 10 minute duration.

Infants were randomly assigned to one of two groups. Infants in the Control group received routine NICU nursing care. Infants in the Intervention group received routine NICU care as well as 10 minutes of exposure to their mothers recorded voice every day

for 14 days. Infants in the two groups were evaluated and observed for 30 minutes every day for 14 days. Heart rates, respiratory rates and oxygen saturation levels as displayed on the monitor were recorded every minute for 30 minutes. Behavioral score (BIIP) was measured at every 10 minute. Weight gain was measured every other day by a standardized digital weight scale. Infants were evaluated during 3 phases: 10 minute baseline, 10 minute intervention and 10 minute post intervention.

Result

A total of 138 patients completed the study. There was significant reduction of mean heart rate over time [F=5.071, p<0.05] and median respiratory rate over time (Z = -7.27, p < 0.01) in the intervention group. There was significant difference in median respiratory rate in intervention group (Z = -4.39, -4.23,-4.15, p <0.01) compared to control group. There was also significant increase of oxygen saturation in intervention group (Z = -2.14, -2.39, -2.56 p < 0.05). There was no significant difference in mean weight gain between intervention and control group [MD 0.30 (-1.9, 2.5), P>0.05]. There was no significant changes of Behavioral Indicator of Infant Pain profile (BIIP) with regard to time [Z = -0.31, -0.36, -0.65 P >0.05].

Conclusion

This study showed that exposure to mother's voice had positive effect on premature infant's heart rate, respiratory rate and oxygen saturation while no changes on mean weight gain and behavioral score with no adverse reaction noted during intervention.

MAKLUMAT PENYELIDIKAN

Tajuk Penyelidikan: **Kesan suara ibu pada fisiologi dan tingkah laku di kalangan bayi pra-matang : Penyelidikan terkawal rawak**

Nama penyelidik: Dr Nurul Amani Abd Ghani (MMC No 47326)

PENGENALAN

Anda dijemput untuk mengambil bahagian secara sukarela dalam kajian penyelidikan bertajuk **Kesan suara ibu pada fisiologi dan tingkah laku di kalangan bayi pra-matang: Penyelidikan terkawal rawak.** Sebelum anda bersetuju untuk menyertai kajian ini, adalah penting untuk anda membaca dan memahami tujuan penyelidikan ini. Jika anda mengambil keputusan untuk menyertai, anda akan menerima borang ini untuk disimpan sebagai rekod anda.

Bayi pra-matang yang dilahirkan mesti kekal dalam NICU sehingga tindak balas deria dan fisiologi mereka menjadi betul maju. Telah diketahui bahawa tahap bunyi di NICU adalah punca utama tekanan persekitaran untuk bayi pra-matang. Suara ibu yang biasa bayi dengari dari dalam rahim di persekitaran NICU boleh menyediakan suatu domain penting dalam keselarasan, keselamatan, dan keselesaan yang sukar untuk ditiru.

TUJUAN PENYELIDIKAN

Kajian ini dijalankan untuk membandingkan kesan suara ibu berbanding bunyi sekitar NICU pada keadaan fisiologi dan tingkah laku di kalangan bayi pra-matang. Kajian ini juga bertujuan untuk membandingkan kenaikan berat badan di kalangan bayi pra-matang terdedah kepada suara ibu berbanding bayi yang terdedah kepada persekitaran NICU sahaja.

KELAYAKAN UNTUK MENYERTAI

Kajian ini bertujuan untuk melibatkan semua bayi pra-matang dari usia kehamilan 27 minggu hingga 35 minggu yang dimasukkan ke NICU Hospital Sultanah Bahiyah dari Oktober 2014 hingga Mac 2015 Dianggarkan sebanyak 140 bayi pra-matang akan mendaftar dalam tempoh kajian ini.

PROSEDUR PENYELIDIKAN

Semua bayi pra-matang yang memenuhi kriteria kemasukan penyelidikan akan dimasukkan untuk kajian ini. Anda akan diberikan sebuah perakam suara di permulaan pengajian. Anda akan diminta untuk menyanyikan lagu bayi pilihan anda mengikut pilihan anda untuk jumlah masa rakaman 10 minit.

Bayi anda akan didedahkan dengan rakaman ini selama 10 minit setiap hari selama 2 minggu. Setiap sesi pengajian akan mengambil masa lebih kurang 30 min. Parameter fisiologi bayi anda akan diawasi dalam setiap sesi. Berat badan akan dipantau setiap selang sehari sehingga tamat tempoh penyelidikan selama 2 minggu.

RISIKO

Satu alat pengukur tahap bunyi akan digunakan untuk menentukan kekuatan rakaman suara yang dimainkan untuk memastikan ia mengikuti cadangan dari American Academy of Pediatrics. Tiada risiko yang dikenalpasti untuk bayi anda sepanjang pengetahuan kami setakat ini. Bayi anda akan melalui pemeriksaan pendengaran standard oleh pakar audiologi sebelum keluar dari hospital dan bayi anda juga akan membuat rawatan susulan di klinik Pediatrik di Hospital Sultanah Bahiyah sehingga berumur 2 tahun sebagai standard penjagaan untuk bayi pra-matang. Anak anda akan dirujuk kepada pakar ENT (Telinga, hidung & tekak) sekiranya kelainan dikesan daripada penilaian pendengaran untuk nasihat selanjutnya.

PENYERTAAN DALAM PENYELIDIKAN

Penyertaan anda dalam kajian ini adalah secara sukarela. Anda boleh menolak untuk mengambil bahagian dalam kajian ini atau anda boleh menamatkan penyertaan dalam kajian ini pada bila-bila masa, tanpa sebarang penalti atau kehilangan manfaat perubatan yang sepatutnya anda perolehi. Penyertaan anda mungkin juga diberhentikan oleh doktor kajian atau penaja tanpa persetujuan anda. Anda juga tidak akan dikenakan apa- apa bayaran atau perbelanjan berkaitan kajian ini.

MANFAAT YANG MUNGKIN DIPEROLEHI

Hasil dan maklumat daripada kajian ini akan menambah pengetahuan lanjut tentang penjagaan bayi pra-matang dan dengan itu akan membantu doktor untuk memperbaiki dan mengoptimumkan penjagaan bayi pra-matang pada masa akan datang.

PERTANYAAN

Jika anda mempunyai sebarang soalan mengenai prosedur kajian ini atau hak-hak anda, sila hubungi:

Dr Nurul Amani Abd Ghani (MMC No 47326)

Jabatan Pediatrik ,Pusat Pengajian Sains perubatan

USM kampus Kesihatan, Kubang Kerian Kelantan

Tel No: 0124287558

Jika anda mempunyai sebarang soalan berkaitan kelulusan Etika, sila hubungi:

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Tel: 03- 2282 9082/9085
03- 2287 4032/03-22820491

KERAHSIAAN

Maklumat peribadi anda dan maklum balas akan dirahsiakan oleh para penyelidik dan kakitangan kajian dan tidak akan dibuat secara umum melainkan jika diperlukan oleh undang-undang.

Data yang diperolehi dari kajian akan diterbitkan untuk tujuan pengetahuan tetapi data ini tidak akan mendedahkan maklumat individu pesakit yang terlibat dalam kajian ini. Maklumat peribadi anda dan rekod perubatan akan disimpan dan diproses pada komputer.

Dengan menandatangani borang persetujuan ini, anda membenarkan penelitian rekod, penyimpanan maklumat dan data pemindahan seperti yang dinyatakan di atas.

TANDATANGAN

Untuk menyertai kajian ini, anda atau wakil anda mesti menandatangani persetujuan di halaman tandatangan.

BORANG KEBENARAN UNTUK PROJEK PENYELIDIKAN

Tajuk : **Kesan suara ibu pada fisiologi dan tingkah laku di kalangan bayi pra-matang : Penyelidikan terkawal rawak**

Penyelidik: Dr Nurul Amani Abd Ghani (MPM 47326)

Saya telah membaca dan memahami maklumat yang berkaitan dengan projek penyelidikan dan kajian telah menjelaskan kepada saya. Semua soalan-soalan saya mengenai kajian ini telah menjawab sepenuhnya oleh doktor.

Saya juga faham bahawa penyertaan saya dalam kajian ini adalah secara sukarela dan saya boleh menarik diri pada bila-bila masa. Keputusan saya untuk menyertai atau menarik diri daripada kajian ini tidak akan mempengaruhi atau memberi kesan pada rawatan yang saya terima sekarang. Saya, secara sukarela memberi kebenaran untuk mengambil bahagian dalam kajian ini.

Penyelidik:

Nama :_____ NRIC :_____

Tandatangan :_____ Tarikh :_____

Waris/Penjaga:

Nama :_____ NRIC :_____

Tandatangan :_____ Hubungan :_____

Tarikh :_____

Saksi:

Nama :_____ NRIC :_____

Tandatangan :_____ Tarikh :_____

RESEARCH INFORMATION

Research Title: **Effect of maternal voice on physiological and behavioral measures in premature infants : A Randomized Controlled Trial**

Researchers Name: Dr Nurul Amani Abd Ghani (MMC No 47326)

INTRODUCTION

You are invited to take part voluntarily in a research study entitled Effect of maternal voice on physiological and behavioral measures in premature infants : A Randomized Controlled Trial. Before agreeing to participate in this study, it is important that you read and understand this research information form. If you decided to participate, you will receive this form to keep for your records.

Premature babies who are born must remain in NICU until their sensory and physiological responses become properly developed. It is known that sound level in NICU is a major source of environmental stress for premature infants. Vocal familiarity within the infant's sound environment may provide an essential domain of consistency, security, and comfort that is difficult to replicate.

PURPOSE OF STUDY

This study is conducted to compare the effect of maternal voice against NICU environmental sounds on physiological and behavioral measures in premature infants. This study also aim to compare weight gain among premature infants exposed to maternal voice compared to babies exposed to NICU environment only.

QUALIFICATION TO PARTICIPATE

This study aim to involve all premature baby from gestation age of 27 week to 35 week who is admitted to NICU Hospital Sultanah Bahiyah from October 2014 till Mac 2015. An estimation of 140 premature babies will be enrolled during this study period.

STUDY PROCEDURE

All premature infant who fulfill inclusion criteria will be enrolled to this study. You will be given a voice recorder at the starting of study. You will be asked to sing infant lullaby of your choice according to your preference for total recording time of 10 minutes.

Your infant will be exposed to your recorded lullaby 10 minutes every day for 2 weeks. Each session of study will take about 30 min. Your infant physiological parameters will be monitored in each session. His weight gain will be monitored every alternate day until completion of study.

RISKS

A sound level meter will be used to determine intensity of voice recording playback to ensure it follows recommendation from American Academy of Pediatrics. There is no known risk to your infant as the best of knowledge so far. Your infant will undergo standard hearing assessment by audiologist before discharge from hospital and your infant also will be follow up in Paediatric clinic in Hospital Sultanah Bahiyah for up to 2 years old as standard of care for premature infant. Your child will be referred to ENT (Ear, nose & throat) specialist should any abnormality detected from hearing assessment for further management.

PARTICIPATION IN THE STUDY

Your participation in this study is entirely voluntary. You may refuse to take part in the study or you may stop participation in the study at anytime, without a penalty or loss of benefits to which you are otherwise entitled. Your participation also may be stopped by study doctor or sponsor without your consent. You will not be charged any expenses pertaining this study treatment and procedure.

POSSIBLE BENEFITS

The outcome and information from this study will add further information about care of premature infant and thus will help clinicians to further improve and optimizing care of premature infant.

QUESTIONS

If you have any question about this study or your rights, please contact:

Dr Nurul Amani Abd Ghani (MMC No 47326)

Department of Pediatrics

School of medical Sciences

USM Health campus, Kubang Kerian

Kelantan

Tel No : 0124287558

If you have any questions regarding Ethical Approval, please contact:

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
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KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Tel: 03- 2282 9082/9085
03- 2287 4032/03-22820491

CONFIDENTIALITY

Your personal information and responses will be kept confidential by the study researchers and staffs and will not be made publicly available unless disclosure is required by law.

Data obtained from this study that does not identify you as individually will be published for knowledge purposes. Your personal information and medical records may be held and processed on a computer.

By signing this consent form, you authorize the record review, information storage and data transfer as described above.

SIGNATURES

To participate in this study, you or your representative must sign and date the signature page.

CONSENT FORM FOR RESEARCH PROECT

Title: **Effect of maternal voice on physiological and behavioral measures in premature infants : A Randomized Controlled Trial**

Researcher: Dr Nurul Amani Abd Ghani (MPM 47326)

I have read and understood the information regarding the research project and the study has been explained to me. All my questions about the study have been fully answered by the doctor.

I also understood that my participation in this study is entirely voluntary and I can withdraw at anytime. My decision to participate or withdraw from the study will not influence or affect the care that received now. I voluntarily give my consent to participate in this study.

Researcher:

Name :_____ NRIC :_____

Signature :_____ Date :_____

Legal guardian:

Name :_____ NRIC :_____

Signature :_____ Relationship :_____

Date :_____

Witness:

Name :_____ NRIC :_____

Signature :_____ Date :_____

CHAPTER 1 : INTRODUCTION

1.1 PRETERM INFANTS

Preterm infants lose significant contact with their mothers' voices during prenatal development and nursed in hospital environment that exposed them to elevated light and sound levels in NICU. Thus, they are not only deprived of the protective properties of womb, but of a possibly critical aspect for normal development that is the mother's voice (Krueger, 2010).

Premature infants usually remains in an enclosed incubator where touching and sensory stimulation are restricted until they are grown enough to withstand normal environment. Ambient auditory stimuli from the surrounding NICU environment can occur frequently, spike unpredictably, and can have unwanted consequences for the neonate (Standley 2000).

1.2 HEARING DEVELOPMENT IN INFANT

The development of the auditory system is an elaborate process that begins very early in gestation. All major structures of the ear, including the cochlea, are in place between 23 and 25 weeks gestational age (Hall 3rd, 2000).

The human fetus can perceive and react to auditory information starting at approximately week 26 of life (Ruben, 1991). Thus, most preterm infants can already hear when they first admitted to the NICU.

Hair cells in the cochlea are tuned for specific frequencies and can translate vibratory acoustic stimuli into an electrical signal that is sent to the brainstem between 26 and 30 weeks gestational age (Querleu et al., 1989). The auditory system is mature enough to permit complex sounds and distinguish between different speech phoneme after 30weeks gestational age (Hepper et al.,1993). Finally, by 35 weeks GA, auditory processing facilitates learning and memory formation (Moon and Fifer, 2000). Hence, there is a need to protect preterm newborns earlier on from auditory stimuli they are not yet ready to handle (Als et al., 2005).

1.3 NICU NOISE AND STRESS RELATED BEHAVIOUR

American Academy of Pediatrics (AAP) recommended noise level exceeding 45 dB is best avoided for infants in NICU based on proposal by the US Environmental Protection Agency (Etzel et al., 1997). A review article by Graven also recommended that noise levels should not exceed 50 to 55 dB in the NICU (Graven, 2000).

However, many studies have proved that noise levels were found to be above the AAP recommended 45-dB level and often louder than the 50-dB level, which should not be exceeded more than 10% of the time (Darcy et al., 2008, Levy et al., 2003). The recommended impulse maximum of 65 dB was also exceeded (Darcy et al., 2008).

A study by Levy have reported that NICU sounds average between 50 and 90 dB with mean noise amounts were significantly higher in Level III (subspecialty neonatal care) NICUs compared to Level II (specialty neonatal care) NICUs (Levy et al., 2003).

1.4 STRESS AND BIOPHYSICAL PROFILE

It is well known that sound levels in the NICU are a major source of environmental stress for premature infants (Peng et al., 2013). The most common indicators of physiological stress and pain are similar and include changes in heart rate, respiratory rate, blood pressure, transcutaneous oxygen levels, oxygen saturation, intracranial pressure, vagal tone, skin blood flow, and palmar sweat. (Holditch-Davis et al., 2003, Hall et al., 1996)

Peng et al demonstrate positive relationship between environmental stressors (light, noise, handling, and painful procedure) and changes in physiological signals. There were also positive relationships between environmental stress and some specific stress behaviors (grimace, hand to mouth, holding on, sucking, finger splay, salute, sitting on air, and yawn). Hence, recognizing the preterm infant's biological stress responses to environmental stressors is important, allowing for early interventions to reduce the possibility of more serious physiological or pathological changes the preterm infant. (Peng et al., 2009)

Studies have indicated that increased noise levels are associated with increased fatigue, stress behaviors, hyper alerting responses, startle, hypoxemia, agitation, crying, sleep interruptions, and intracranial pressure in neonates. (Standley, 1991, Caine, 1991).

1.5 SOUND AND BIOPHYSICAL PROFILE

Research in NICU practice supports the use of music not only for recovery from painful procedures (Tramo et al., 2011, Hartling et al., 2009), but also in critical areas such as sucking (Yildiz and Arikan, 2012), weight gain (Kemper and Hamilton, 2008), and sleep (Arnon et al., 2006).

A study by Coleman comparing effect of talking, singing and environmental noise to biophysical profile of premature infants showed singing lowered HR, increased oxygen saturation, and reduced distress behavior. These infant also leave NICU 3 days earlier, had higher calorie intake and higher weight gain (Coleman et al., 1997).

An RCT by Loewy involving 272 premature infants comparing effects of 3 live music interventions (heart rhythm, breathing rhythm and lullaby of parental choice) towards physiologic function (heart and respiratory rates, O2 saturation levels, and activity levels) and developmental function (sleep, feeding behavior, and weight gain) in premature infants found lower HR occurred during the lullaby and rhythm intervention. Sucking behavior, sleep patterns and caloric intake also improved with rhythm intervention. Music also shown to decreased parental stress perception (Loewy et al., 2013).

Similar respond was found as decrease in respiratory rate and increase in oxygen saturation in preterm infants exposed to recorded lullaby though there is no significant difference in heart rate and weight gain (Habibollah and Mohammadzadeh, 2010).

However, Arnon et al found that live music therapy is associated with a reduced heart rate and a deeper sleep at 30 minutes after therapy in stable preterm infants compared to recorded music or no music therapy. Both recorded and no music therapies had no significant effect on the tested physiological and behavioral parameters (Arnon et al., 2006).

Exposure to Mozart music significantly lowers Resting Energy Expenditure (REE) in healthy preterm infants thus might explain the improved weight gain (Lubetzky et al., 2010).

Beside live and recorded music, Quranic verse had been used for study in premature infants. A study of 120 premature infants who had been exposed to 20 minutes of quranic verse recording showed significant changes in mean of respiratory and heart rate significantly decreased and oxygen saturation levels increased in Quran group and changes continued up to 10 minutes after intervention (Keshavars et al., 2010).

A study by Alipour comparing mean physiological response and behavioral state in 120 premature infants exposed to Quranic verse, lullaby and NICU environment sound. Although fluctuations were observed in the mean of physiological responses and behavioral states in premature infants who listened to the recitation of the holy Quran and lullaby music, but these fluctuations were not significant and the preterm infants did not display any adverse reactions (Alipour et al., 2013).

1.6 PREMATURE INFANTS AND THEIR MOTHER

Preterm infants had lost important auditory stimulation from their mother's voice amidst unfiltered levels of auditory stimuli in NICU. While in uterine environment, the fetus receives multiple forms of sensory stimulation not only hears her voice, but feels her vertebral column and diaphragm gently vibrate and move in sync with her voice at appropriate time throughout the gestation that is very crucial in growth and development (Krueger, 2010).

2 studies had proven that family involvement and maternal visitation had major impact on premature infants as it decreased length of hospitalization and NICU stay (Zeskind and Iacino, 1984, Melnyk et al., 2006). In a family who can't afford to visit regularly, a familiar vocal within infant's hearing environment may provide an important domain of consistency, security, and comfort that even the most modern NICUs cannot replicate (Loewy et al., 2013).

Comparing acoustic stimulation with maternal voice, maternal voice not only induce significant heart rate variability but it also producing lasting effect post intervention (Djordjevic, 2010). Recent study showed that mother's voice reduces arterial blood sampling induced pain in the term neonates (Azarmnejad, 2015).

Maternal vocal stimulation not only revealed significantly greater oxygen saturation level, stable heart rate and fewer negative critical events but there is also comparable effects of maternal talk and singing on infant behavioral state encouraging maternal interaction with their preterm infants (Filippa et al., 2013).

Another study showed overall decreasing trend in cardio respiratory events with age when infants were exposed to maternal sound stimulation (MSS) versus Routine Hospital Sound suggesting an effective therapeutic window for MSS when the infant's auditory brain development is most intact (Doheny et al., 2012).

Studies have shown that preterm infants who were exposed to an audio recording of their mother's voice achieved full enteral feed quicker and showed meaningful changes in heart rate compared to age-matched controls receiving routine care (Krueger et al., 2010).

Picciolini et al studied 71 premature infants with effect of the exposure to maternal voice, administered via bone conduction, on preterm infants autonomic and neurobehavioral development. Treatment group had lower heart rate, higher proportion of stable skin color; higher visual attention performance and quality of the general movements at term were better compared to control. Neurofunctional assessment score at 3 months of corrected age was higher in the treatment group while no difference detected at 6 months of corrected age (Picciolini et al., 2014).

Caskey et al had found that exposure to parental talk was a significantly stronger predictor of infant vocalizations at 32 weeks and conversational turns at 32 and 36 weeks thus highlighting powerful impact that parent talk has on increment of vocalizations in preterm infants in the NICU (Caskey et al., 2011).

1.7 NEUROBEHAVIORAL SCORE

Premature infants undergo multiple painful diagnostic and therapeutic procedures to ensure their survival. Accurate assessment of pain is necessary in order to provide appropriate pain management and preventive measures of procedural pain (Anand et al., 2005). Assessment of pain and stress in preterm infants are difficult and complex because clinicians are limited to indirect measures of pain responses as infants unable to self report (Morison et al., 2001).

Infant pain responses consist of both behavioral and physiological components, dissociations between behavioral and physiological pain. Physiologic indicators of pain include changes in heart rate, respiratory rate, blood pressure, oxygen saturation while behavioral indicators include changes in facial expressions, body movements, and crying, but these may be absent in some neonates who are neurologically impaired or pharmacologically paralyzed (Pediatrics et al., 2006, Morison et al., 2001).

A number of scales have been developed for assessing acute pain in preterm infants; few have had adequate psychometric validation (Duhn and Medves, 2004). Currently, the two scales used most widely used are the Neonatal Infant Pain Scale (NIPS) (Lawrence et al., 1993) and the Premature Infant Pain Profile (PIPP) (Stevens et al., 1996). The NIPS includes crying as one of the indicators, but many preterm infants require mechanical ventilation, a procedure which precludes using cry as an indicator. Furthermore, the extremity action descriptors on the NIPS are very general. On the other hand, the PIPP (Stevens et al., 1996) uses weightings to adjust for varying gestational ages and sleep/wake states to accommodate these contextual factors. However, the weightings

applied to the scoring of the sleep/wake states, in particular, may obscure important information related to infant arousal (Holsti and Grunau, 2007).

Unlike facial responses, hand and other body movements are heightened in infants who have had greater exposure to painful procedures or when handling is clustered (Holsti and Grunau, 2007). The Behavioral Indicators of Infant Pain (BIIP) was designed to capture the behavioral pain cues of hospitalized neonates both preterm and full-term. Its score based on facial and hand movement of premature infant. BIIP score ranges from 0 to 9 with increasing pain severity on bigger score. BIIP was developed by Holsti and Grunau in 2007 with initial validation was done on 92 preterm infants who undergone invasive skin breaking procedure while in NICU. One hundred assessments were done between score of BIIP and NIPS. Scores on the BIIP changed significantly across Phases of blood collection ($p < 0.01$) with high internal consistency (0.82) and inter-rater reliability (0.80-0.92). The BIIP has been shown to be a reliable, valid scale for assessing acute pain in preterm infants in the NICU (Holsti et al., 2008).

The BIIP scale is reliable, accurate, and valid assessment for measuring acute pain in preterm infants in the NICU. This assessment combines the relatively most specific, anatomically based, theoretically derived indicators; and it allows evaluation of behavioral and physiologic pain responses separately (Holsti et al., 2008).

CHAPTER 2 : OBJECTIVES

2.1 GENERAL OBJECTIVE

To determine the effect of maternal voice vs NICU environmental sounds on physiological and behavioral measures in premature infants.

2.2.1 SPECIFIC OBJECTIVE

2.2.2 To compare mean Heart Rate, Respiratory Rate, Oxygen saturation in infants exposed to mother's voice vs NICU environmental sound.

2.2.3 To compare mean weight gain between premature infants exposed to mother's voice vs NICU environmental sound

2.2.4 To compare mean neurobehavioral score between premature infants exposed to mother's voice vs NICU environmental sound

2.3 RESEARCH HYPOTHESIS

The research hypothesis are: there are effects of maternal voice vs NICU environmental sounds on physiological and behavioral measures in premature infants generally. There are significant mean changes of heart rates, respiratory rate and oxygen saturation in premature infants exposed to mother's voice (intervention) compared to NICU environment (control) only. There is significant weight gain in intervention group compared to control group. There is a significant change of neurobehavioral score in intervention group compared to control.

CHAPTER 3 : METHODOLOGY

3.1 TRIAL DESIGN

This is a parallel randomized control trial with 1:1 allocation ratio conducted in NICU Hospital Sultanah Bahiyah (HSB), Alor Setar from June 2015 to Nov 2015.

3.2 PARTICIPANTS

Eligible participants were all premature infant who had been admitted to NICU HSB from June 2015 to Nov 2015 who met the inclusion criteria as below:

1. Corrected gestational age 27-35 weeks AND
2. Already on full feeding of at least 120cc/kg/day AND
3. Nursed in closed incubator (isolette)

While premature infants with these exclusion criteria were excluded:

1. Require mechanical ventilation
2. Medically unstable : HIE, NEC, sepsis, on inotropic support
3. Born with major congenital anomalies
4. Still requiring intravenous drip or parenteral nutrition

Any premature infants who were recruited into the study need to be dropout if they:

1. Need to be ventilated during study period
2. Need to be kept nil by mouth during study period
3. Become medically unstable determined by treating clinician: HIE, NEC, sepsis, on inotropes

3.3 SETTINGS

This study took place in NICU Hospital Sultanah Bahiyah, Alor Setar. This is the biggest tertiary referral hospital in Kedah that covers entire Kedah population of approximately 2 million people. It consists of 160 bedded pediatric and neonatal wards with 16 ventilator beds for neonatal ward. This hospital also is one of referral centre in northern area of peninsular Malaysia.

3.4 INTERVENTIONS

All premature infants who fulfilled the eligibility criteria of the study are identified. An appointment for a meeting with parents for consent was arranged via phone or when parents visited the infant. The meeting took place in NICU, Hospital Sultanah Bahiyah, Alor Setar. Parents were given Patient Information Sheet and Informed Consent form during the meeting (APPENDIX 2). After consent was obtained, all infant's mother was asked to sing appropriate lullaby of their choice due to multiracial population. The session was recorded using a voice recorder (SONY ICD-UX543F) for 10 min in predetermine quiet room to minimize sound interference.

Infants were randomly assigned to one of two groups. Infants in the Control group received routine NICU nursing care. Infants in the Intervention group received routine NICU care as well as 10 minutes of exposure to their mothers recorded voice every day for 14 days. . The decibel levels were tested at the infant's ear using a sound level meter (Mini Digital Decibel Audio Sound Pressure Meter MTR01DASP). Each infant were given feeding and their diapers were changed within half an hour before the intervention.

Infants in the two groups were evaluated and observed for 30 minutes every day for 14 days. Heart rates, respiratory rates and oxygen saturation levels as displayed on the monitor were recorded every minute for 30 minutes. Behavioral score (BIIP) was measured at every 10 minute. Weight gain was measured every other day by a standardized digital weight scale. Neonates were evaluated during 3 phases: 10 minute baseline, 10 minute intervention and 10 minute post intervention. During the phase of 10 minute intervention, the recorded mother's voice was played for the music group while

no recording was played for control group. The recorded mother's voice was discontinued during the 10 minute post intervention and the infant was continued to be observed by the researcher till completion of session.

3.5 OUTCOMES

The primary outcome of this study was to determine the effect of maternal voice on physiological status of premature infants while secondary objectives were to determine the effect of mother's voice on premature infant's weight gain and behavioral measures. Physiological parameters were recorded every minute while weight gains were monitored every alternate day for 2 weeks using a standard weighing machine. Physiological parameters were measured and digitally recorded by using patient monitors (Phillip Intellivue MP70, USA) and weights were measured on a standard digital weighing machine in NICU (SECA 728 baby scales, Germany).

Serial neurobehavioral score were done using Behavioral Indicators of Infant Pain (BIIP) at pre, during and post intervention (Holsti and Grunau, 2007). The scoring was done by bedside by 1 trained person. Prior to starting of study, a pre test scoring was done between 3 allocated trained person to achieve inter rater agreement. The 3 trained person had underwent training for BIIP scoring by watching video tutorial and practical session using BIIP manual provided by Dr Lisa Holsti (Holsti and Grunau, 2007) (Appendix)

3 allocated trained persons are in charge in doing the scoring for the purpose of this study. Inter rater reliability analysis of individual event scores of the BIIP yielded reliability coefficients of 0.81-0.93. Behavioral Indicators of Infant Pain (BIIP) score were measured 3 times per session (pre, during and post intervention).All subjects will undergo hearing assessment prior to discharge from NICU. Clinical data to be entered into a standard proforma sheet include: Demographic data, Gestational age, Heart Rate, Respiratory rate, SpO_2, Weight gain, Behavioral Indicators of Infant Pain (BIIP) score.

3.6 SAMPLE SIZE

Sample sizes were calculated based on all outcome parameters that were heart rate, respiratory rate, oxygen saturation, behavioral score and mean weight gain. Sample size was calculated using two means formula as stated below. The power of study was determine at 0.8, with alpha level of 0.05. The sample size generated was then added with 20% drop out.

$$\mathbf{n} = \frac{2\sigma^2}{\Delta^2}[Z\alpha + Z\beta]^2$$

Table 3.1: Sample size calculation using two means formula

Parameter	Reference	Mean Difference	SD	n + 20%
Heart rate (HR)	(Alipour et al., 2013)	5	9.57	140
Respiratory rate (RR)	(Alipour et al., 2013)	3	5.33	120
Oxygen saturation (SPO_2)	(Alipour et al., 2013)	3	3.25	43
Weight gain	(Farhat et al., 2010)	20	31.8	96
Behavioral score	(Alipour et al., 2013)	1	1.12	48

Therefore the total sample size needed based on highest sample size needed was 140 subjects.

3.7 RANDOMIZATION

A computer generated list of random numbers was used for allocations of participants using computer software 'Research Randomizer' (www.randomizer.org). All subjects were randomized into two groups that were Intervention and Control by block randomization with 1:1 allocation using random block size of 2 sets of 70 unique numbers per set. The concealment of allocation from researcher's enrolling participant was ensured using sealed and opaque envelope. Coding systems was used instead of real name to identify each infant.

All subject's data was kept in a secured and separate cabinet locked in the department room of the investigator in Hospital Sultanah Bahiyah. Once consent was obtained from the parents, an allocated medical officer who was not involved as an investigators would open the sealed envelope and record the allocated group of the subjects. The details of allocated group were unknown to any of the investigators. This officer was also in charge of turning the voice recorder on or off throughout the study. The investigators were kept blinded to the allocation.

3.8 STATISTICAL ANALYSIS

All data were entered cleaned and analyze using SPSS version 20. In descriptive analysis, normal distribution was checked using histogram with underlying normal curve. Numerical data was expressed using Mean (SD) or median (IqR) depending on the distribution. Independent t-test would be used to compare baseline data between the two groups.

Repeated measure ANOVA was used to determine mean difference for time effect (within group) and treatment effect (between groups). Assumptions for RM ANOVA were checked (Normality of residuals, Homogeneity of variance, Assumption of compound symmetry).

If the assumptions were not met, other non parametric test equivalent to RM ANOVA would be used to analyze the data. Friedman test would be used to determine time effect followed by Wilcoxon Sign Rank test for determining time effect within groups. Mann Whitney test would be used to determine treatment effect between groups. Significance level was taken at 0.05.

Inter rater reliability was calculated using Intraclass Correlation Coefficient (ICC) looking at absolute agreement between 3 researches scoring for BIIP.

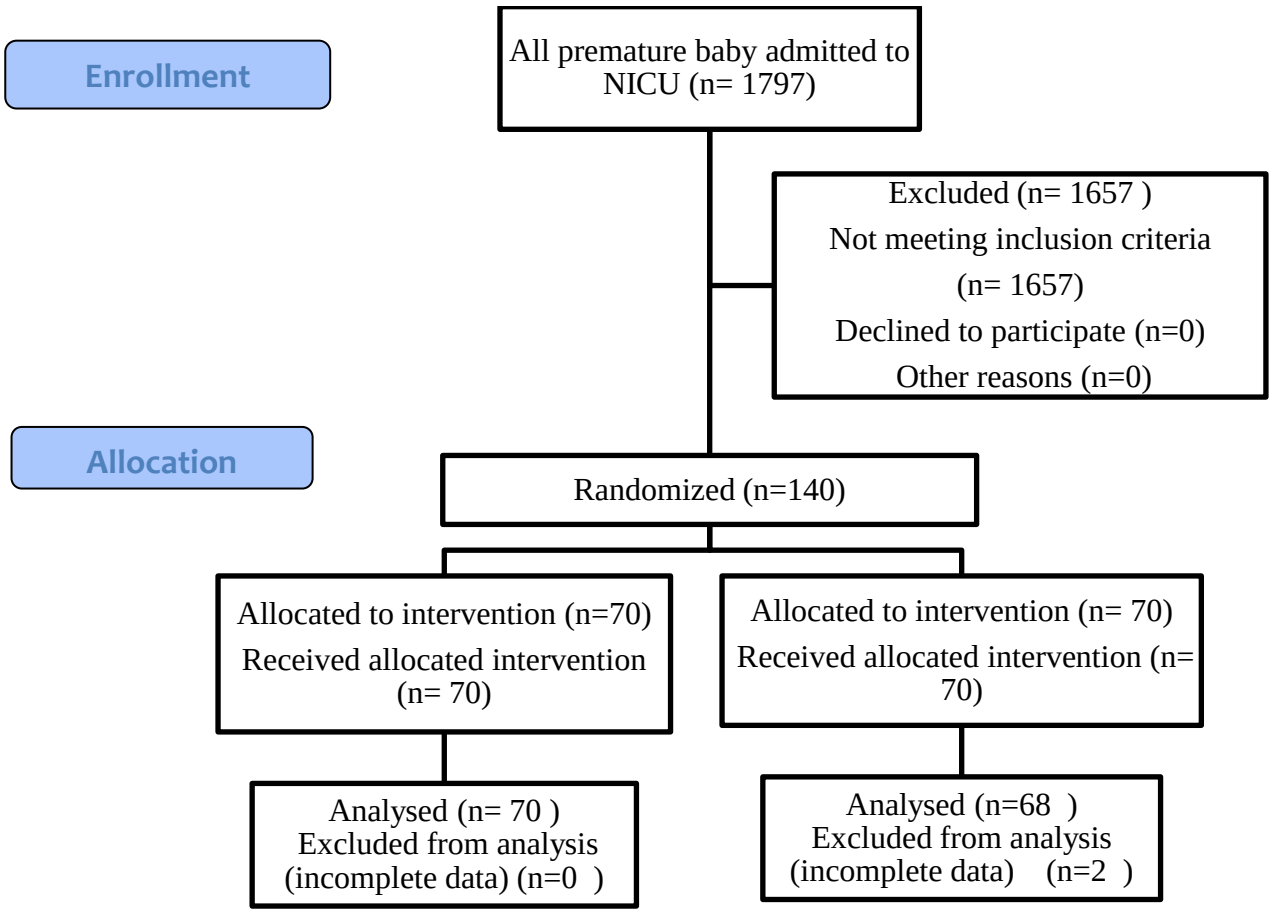
3.9 ETHICAL ISSUES

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Conference on Harmonization (ICH) Good Clinical Practice (GCP). All investigators were GCP certified prior to study beginning. This study was approved by Medical Research and Ethics Committee, Ministry of Health Malaysia on 19 Mac 2015 with registration number NMRR-13-1702-18906(IIR). This study was also registered in Australian New Zealand Clinical Trial (ANZCTR) registry with registration number ACTRN12615000722594

To the best of knowledge now, there was no documented complication in terms of intervention. The infant had undergo standard hearing assessment by audiologist before discharge from hospital and follow up in Paediatric clinic in Hospital Sultanah Bahiyah for up to 2 years old as standard of care for premature infant. The infant would be referred to ENT (Ear, nose & throat) specialist should any abnormality detected from hearing assessment for further management.

3.10 : FLOW DIAGRAM

All premature infant with corrected gestational age 27 week to 35 week who had been admitted to Hospital Sultanah Bahiyah, Alor Setar Kedah. All participants were recruited from 1st June 2015 till completion of study on 20th November 2015. A total of 140 infants were recruited into study but 2 infants were excluded due to incomplete data.



CHAPTER 4: RESULTS

Table 4.1 : Baseline data of the studied premature infants

Variables at enrollment	Intervention (n=70) Mean (SD)	Control (n=68) Mean (SD)	p-value[a]
Age (days)	18.9 (17)	19.4 (6.2)	0.814
Corrected Gestational Age (weeks)	32.8(2.5)	33 (1.4)	0.404
Birth Weight (gram)	1388 (309)	1420 (152)	0.438
Weight at enrollment (gram)	1507 (231)	1512 (146)	0.850
NICU environment (dB)	62.9 (2.9)	63.8 (2.3)	0.037

a. Independent t-test p value

Table 1 showed demographic characteristic of the studied premature infant. Total patient studied was 138 subjects. Their mean age were 18.9 (17) days in intervention group and 19.4 (6.2) days in control group. Mean corrected gestational age (CGA) in intervention group is 32.8 (2.5) weeks while in control group was 33 (1.4) weeks. Mean birth weight in intervention group was 1507 (231) gram and 1420 (152) gram in control group. Mean current weight was 1507 (231) gram in intervention group while control group has mean current weight of 1512 (146) gram. Mean NICU environment sound frequency were 62.9 (2.9) dB for intervention group while 63.8 (2.3) dB for control group.

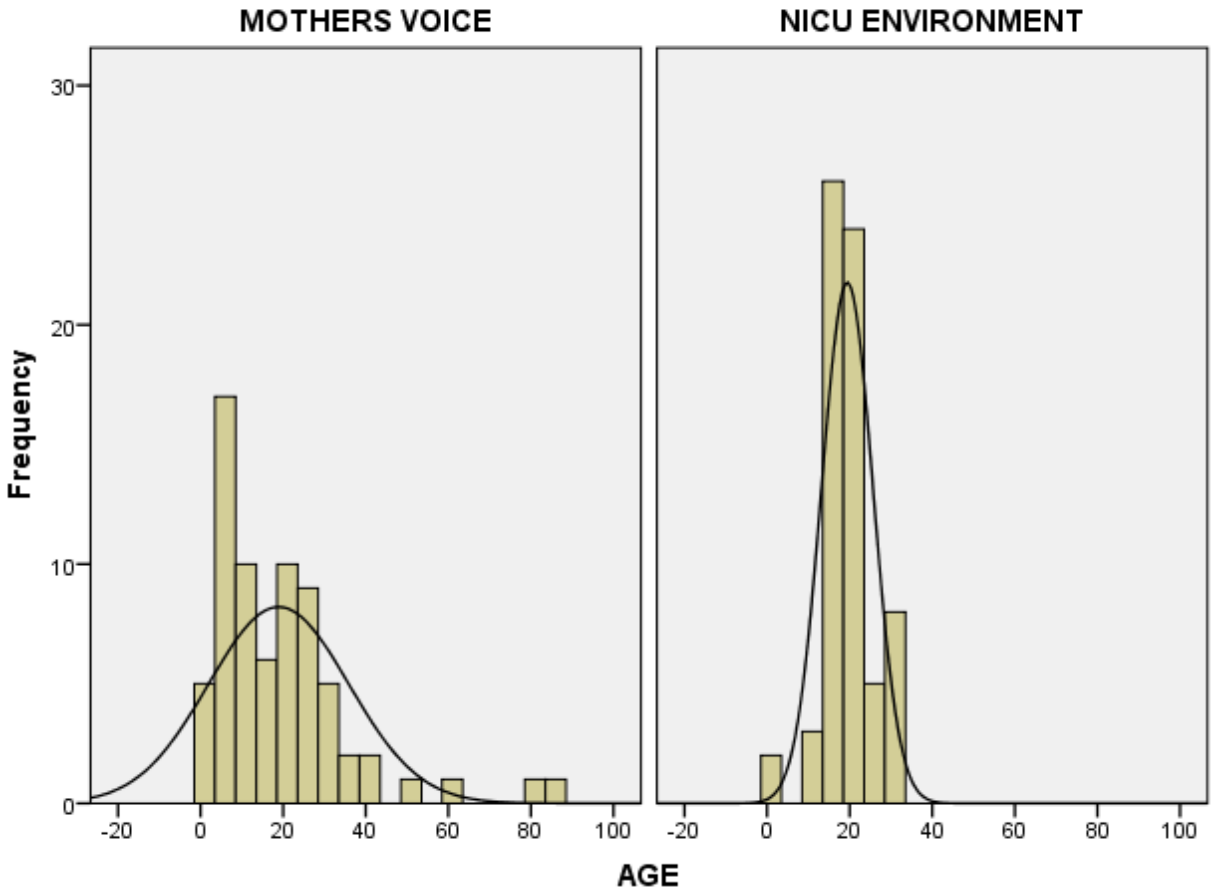


Figure 4.1 : Histogram of premature infant distribution based on age at enrollment

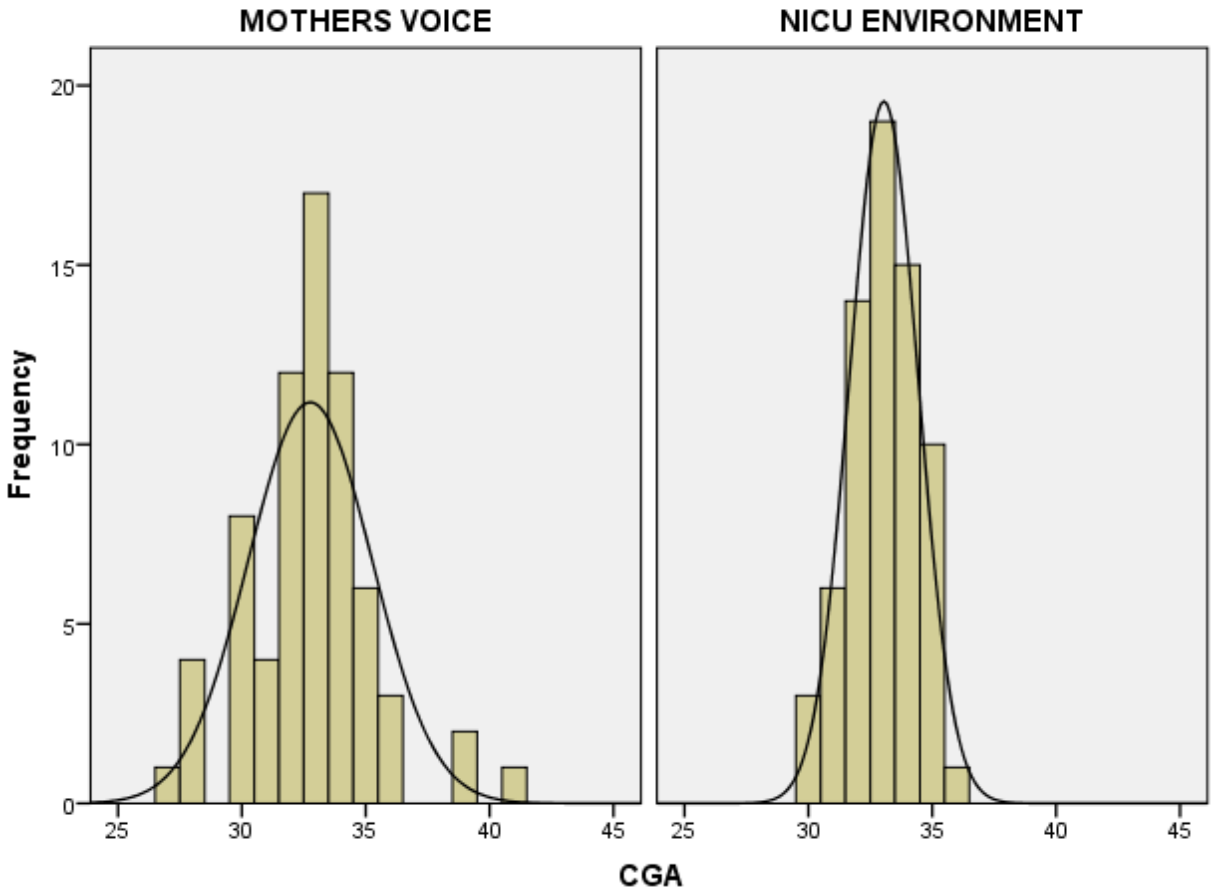


Figure 4.2 : Histogram of premature infant distribution based on corrected gestational age